Sustained release form (retarded release form) comprising alpha-lipoic acid (derivatives)

Description

The present invention relates to a sustained release form (retarded release form) comprising α-lipoic acid (derivatives) and to the use thereof.

α-Lipoic acid (thioctic acid, 1,2-dithiolane-3-pentanoic acid) occurs as a natural product in low concentrations in the form of its R enantiomer in plant and animal cells. Originally discovered as growth factor, the physiological action of α-lipoic acid in hydrophilic and lipophilic media is as coenzyme in the oxidative decarboxylation of α-keto carboxylic acids such as, for example, pyruvates and as antioxidants. In addition, α-lipoic acid serves to regenerate vitamin C, vitamin E, glutathione and coenzyme Q10.

The syntheses of crude racemic α-lipoic acid, of enantiopure R- or S-α-lipoic acid, of dihydrolipoic acid or salts thereof take place in a known or analogous manner as described or summarized, for example, in Crévisy et al., Eur. J. Org. Chem. 1998, 1949, Fadnavis et al., Tetrahedron Asym. 1998, 9, 4109, Dhar et al., J. Org. Chem. 1992, 57, 1699, Adger et al., J. Chem. Soc. Chem. Commun. 1995, 1563, Dasaradhi et al., J. Chem. Soc. Chem. Commun. 1990, 729, Gopalan et al., J. Chem. Soc. Perkin Trans. I 1990, 1897, Yadav et al., J. Sci. Ind. Res. 1990, 49, 400, Tolstikov et al., Bioorg. Khim. 1990, 16, 1670, Gopalan et al., Tetrahedron Lett. 1989, 5705.

The usual method for purifying crude α-lipoic acid is a recrystallization from solvents (e.g. from n-pentane, cyclohexane, methylcyclohexane, ethyl acetate) or mixtures of solvents (e.g. from ethyl acetate and

hexane), as described, for example, in Brookes et al., J. Chem. Soc. Perkin Trans. I 1988, 9, Segre et al., J. Am. Chem. Soc. 1957, 3503, Walton et al., J. Am. Chem. Soc. 1955, 77, 5144, Acker et al., J. Am. Chem. Soc. 1954, 76, 6483. The crystallized α-lipoic acid is then removed by filtration or centrifugation and subsequently dried by conventional methods. The crystalline α-lipoic acid obtained in this way is finally processed further to the active ingredient for use.

Racemic α-lipoic acid has been employed for many years for the treatment of liver disorders, paresthesias and neuropathies (e.g. autonomic and peripheral diabetic polyneuropathy); its use as efficient inhibitor of the replication of HIV-1 viruses has also been suggested (cf. Klin. Wochenschr. 1991, 69(15), 722-724). The racemate of α-lipoic acid also has cytoprotective, antiinflammatory and antinociceptive (analgesic) properties. Moreover, α-lipoic acid is also a radical scavenger which is readily soluble in liphophilic media. Since α-lipoic acid has also been shown to stimulate glucose transport in myocytes and adipocytes (cf. Lipoic Acid in Health and Disease, Marcel Dekker Inc., New York 1997, pp. 87 et seq.) the use of this active ingredient for the treatment of disorders associated with type 2 diabetes is also possible.

Clinical studies of the pharmacokinetics of α-lipoic acid have, however, shown only a very low absolute bioavailability both for the (R) enantiomer, of 24.1-38.2%, and for the (S) enantiomer, of 19.1-28.3%, of α-lipoic acid. Moreover the plasma half-life after oral administration has been observed to be relatively short at less than two hours (Table 1).

Table 1 Pharmacokinetic parameters of α-lipoic acid enantiomers after a single oral dose of various dosage forms (from Hermann and Niebch, Lipoic Acid in Health and Disease, Marcel Dekker, New York 1997, p. 346)

200 mg (±)-lipoic acid		as solution, oral		as 4×50 mg tablets		as 200 mg tablet	
Enantiomer		R	S	R	S	R	S
F[1] [%]	Mean [2]	38.2	28.3	25.9	20.9	24.1	19.1
	σ [3]	± 15.2	± 14.4	± 17.1	± 16.6	± 12.7	± 12.8
C_{max} [µg ml^{-1}]	Mean [2]	2.24	1.32	0.60	0.38	0.49	0.31
	σ [3]	± 1.21	± 0.69	± 0.41	± 0.28	± 0..27	± 0.16
t_{max} [h]	Mean [2]	0.21	0.21	0.70	0.70	0.90	0.90
	σ [3]	± 0.07	± 0.07	± 0.41	± 0.41	± 0.74	± 0.74
$t_{1/2}$ [h]	Mean [2]	0.24	0.15	0.71	0.82	0.33	0.33
	σ [3]	± 0.29	± 0.08	± 0.68	± 0.99	± 0.20	± 0.24

[1] F: bioavailability [2] arithmetic mean [3] standard deviation

Attempts have been made to overcome these disadvantages of unsatisfactory bioavailability and low plasma half-life with the aid of so-called sustained release forms which are intended to ensure delayed release.

Thus, for example, DE-A 44 13 350 discloses a solid slow release form which is in the form of pellets and which, besides a biologically active compound a) ("active substance"), comprises b) also at least one natural, semisynthetic or synthetic polymer which is insoluble in water and in gastrointestinal fluids, c) at least one water-insoluble lipophilic component with plasticizer properties for polymer b) and lubricant properties, d) at least one natural or semisynthetic hydrophilic polymer which is colloidally soluble in water or gastrointestinal fluids, which forms highly viscous solutions or gels or at least swells ("gel former") in water or gastrointestinal fluids, and optionally one or more conventional formulation auxiliaries, the gel formers mentioned being water-insoluble chitin derivatives such as chitosan. The gel former is therefore intended in particular to make it possible for the active substance to diffuse out of the inside of the pellets. A possible active substance which is mentioned among others is thioctic acid (α-lipoic acid).

This slow release form with a very complex composition is in the form of pellets which are obtained by melt extrusion at temperatures between 50 and 200°C, with preference for the so-called hot cut.

The extrusion process must be regarded as disadvantageous with this slow release form - besides its multicomponent polymer composition - especially in relation to α-lipoic acid as active substance.

α-Lipoic acid is known to be a thermally unstable compound, which is why both the temperature of from 50 to 200°C intended for the extrusion process, and the hot cut which is likewise preferred will have adverse effects less on the polymers used but very probably on the possible active α-lipoic acid, which is why serious thermal decomposition is to be assumed in the particular case of α-lipoic acid.

The combination of a hydrophilic and amide-containing polymer with an endogenous compound in a medical composition for producing a topical barrier formulation is disclosed in WO 98/26788. A suitable polymer mentioned is, inter alia, one from the group of native chitosans or catonic derivatives thereof. The polymer must be bound to an anionic scavenger substance, inter alia in the form of the endogenous compound mentioned, which must additionally have an amino and/or thiol function. The main purpose of use of this formulation is for skin disorders with an allergic background.

A formulation for controlled release of α-lipoic acid is also disclosed in WO 99/61004, according to which a therapeutic reactive amount of α-lipoic acid and a binding material are combined so that the lipoic acid is protected from chemical degradation in the gastrointestinal tract and, at the same time, controlled release of the lipoic acid is ensured. The binding material used is an aqueous solution of cellulose acetate phthalate and microcrystalline cellulose. Although the examples cited in this connection show the antidiabetic effect of this formulation via the measured blood glucose level, no proof is given of the asserted sustained release action of α-lipoic acid.

The object of the present invention, derived from the known prior art and, in particular, because of the

disadvantages associated therewith, is thus to develop a sustained release form which comprises α-lipoic acid (derivatives), which makes it possible to improve the bioavailability of α-lipoic acid and/or suitable derivatives thereof and which ensures a plasma level of α-lipoic acid which remains constant for several hours in order thus to be able to improve markedly the therapeutic effect of α-lipoic acid (derivatives). It was additionally intended with the novel sustained release form on the one hand to improve the absorption of α-lipoic acid or suitable derivatives thereof, for example from the gastrointestinal (GI) tract, and on the other hand to ensure a controlled release of active ingredient for more than about eight hours.

This object has been achieved with a sustained release form which comprises (a) one or more cationogenic polymers, (b) α-lipoic acid or/and at least one of its derivatives and (c) at least one acid different from (b), the components (a) and (b) employed favorably being physiologically and pharmacologically acceptable substances. The pH of the complete formulation is preferably 3.0 to 8.5, particularly preferably 4.0 to 7.0. It has surprisingly been found that besides a desired controlled release of active ingredient for more than eight hours and the extended GI transit time there is also faster penetration of the ingredients. However, completely unexpectedly, the sustained release form of the invention is associated with an in part drastic increase in the bioavailability of α-lipoic acid and derivatives thereof.

The present invention thus represents a dosage form with which, through combination of an anionogenic active ingredient such as α-lipoic acid with a special cationogenic carrier matrix, formulations which, because of predominantly ionic interactions between the

two main components, release the active ingredient with a time lag are made available.

Both racemic and enantiopure R-(+)-α-lipoic acid or S-(-)-α-lipoic acid or any mixtures thereof have proved particularly suitable for the sustained release forms of the invention. It is equally possible to employ racemic dihydrolipoic acid (6,8-dimercaptooctanoic acid) or enantiopure S-(+)-dihydrolipoic acid or R-(-)-dihydrolipoic acid or any mixtures thereof. Examples of further lipoic acid derivatives are the sulfoxides (which are also known in the literature under the name "β-lipoic acid") 1,2-dithiolane-1-oxide-3-valeric acid and 1,2-dithiolane-2-oxide-3-valeric acid, each in enantiopure form or in the form of any mixtures or racemates of single regioisomers and/or diastereomers, or all of them. Furthermore, racemic liponamide (thioctamide) or enantiopure S-liponamide or R-liponamide or any mixtures thereof is also suitable.

In a further preferred embodiment of the invention, the α-lipoic acid or dihydrolipoic acid is employed wholly or partly in the form of its salts as anionogenic component together with a cationogenic polymer and the acid component (c). Thus, particularly suitable salts are those comprising cations from the series of alkali metals (such as, for example, sodium or potassium) or alkaline earth metals (such as, for example, calcium or magnesium). However, it is also possible without difficulty to have recourse to other salts of α-lipoic acid, in which case their cations are derived in particular from the series iron, copper, zinc, palladium, vanadium and selenium.

Also extremely suitable for the sustained release forms of the present invention are α-lipoic acid salts which comprise organic cations and, in this case, preferably open-chain or cyclic ammonium compounds such as

benzylammonium, diisopropylammonium, triethylammonium or cyclohexylammonium, and complex cations, where appropriate with a metallic central atom such as, for example, iron(III), chromium(III) or cobalt(II) and neutral, cationic or anionic ligands such as, for example, water, ammonia, carbonyl, cyano or nitroso, or oxo cations such as oxovanadium(V) (VO_2^+) or oxovanadium(IV) (VO^{2+})).

The ionic interactions, which have already been mentioned, between the cationogenic polymer (a) and the α-lipoic acid or derivatives thereof with anionogenic characteristics on the one hand, and the acid component (c) on the other hand are preferably achieved according to the invention by the use of the polymer chitosan (poly-D-glucosamine) or of a chitosan salt (such as, for example, chitosan hydrochloride, acetate or glutamate), or by use of poly-L-lysine, basic lectins (glycoproteins, e.g. from extracts such as phytohemagglutinins) or other basic polypeptides, polysaccharides (such as, for example, hexosamine sugars) or biopolymers of plant, animal or synthetic origin, and any mixtures thereof. In these cases, this mechanism of a delayed active ingredient adhesion can be described and explained on the basis of ionic, dipolar and other intermolecular interactions in principle as shown in Figure 1.

The chitosan which is preferred as cationogenic polymer can be obtained by chemical conversion (deacetylation) from chitin (poly-N-acetyl-D-glucosamine). The natural sources of chitosan include krill and the shells of shrimps, crayfish, lobsters and other representatives of the crustaceans. High molecular weight chitosan with a molecular mass of from 500 000 to 600 000 Dalton and a degree of deacetylation of 80-95% is particularly suitable for use in cosmetic formulations and in food supplements.

The use of chitosan as pharmaceutical for example as anticancer agent, for wound treatment, for arthritis and for gastrointestinal disorders, and for protecting seeds in agriculture is known.

The content of α-lipoic acid component (b) in the sustained release form can be varied within wide limits. However, it has proved to be particularly advantageous to set the proportion by weight of the α-lipoic acid component relative to the total weight of the sustained release form between 0.1 and 99%, in particular between 20 and 90%. The proportion by weight of cationogenic polymer should be set analogous thereto between 0.1 and 90%, and in particular between 5 and 50%.

The proportions of the acid component (c) may also vary widely: thus, proportions of from 0.001 to 80% by weight are provided according to the invention, although proportions of from 0.1 to 50% by weight and in particular proportions of from 0.1 to 25% by weight are to be preferred.

This wide range of proportions is connected not least with the large number of possible acids which are suitable according to the present invention as component (c): thus, organic or inorganic Brönsted acids such as, for example, acetic acid, hydrochloric acid and glutamic acid can be employed just as well as organic or inorganic Lewis acids, from the series of which in particular carbon dioxide, Ca^{2+} and Fe^{2+} are especially suitable.

However, also suitable are complex acids, in particular hexaaquoaluminum(III) $[Al(H_2O)_6^{3+}]$ or hexacyanoiron(II) acid $[H_4(Fe(CN_6)]$, but also polymeric acids, of which polyphosphoric acid (PPA), an isopolyacid such as, for

example, heptamolybdic acid ($H_6Mo_7O_{24}$), or a hetero-polyacid such as, for example, dodecatungstophosphoric acid ($H_3[PW_{12}O_{40}]$) are to be particularly preferred.

Finally, it is also possible in this connection to employ any mixtures of the individual acid forms with one another but also between the individual acid forms.

It is also provided within the framework of the invention to employ conventional formulation aids, which are then, however, to be regarded only as additional optional component. Suitable in this connection are in particular, fillers, lubricants, flow aids, mold release agents, plasticizers, blowing agents, stabilizers, colorants, extenders, binders, disintegrants, wetting agents, glidants or non-stick agents.

From the wide range of possible suitable formulation aids, those suitable as fillers are oxides of magnesium, aluminum, silicon or titanium, microcrystalline cellulose and cellulose powder, starches and derivatives thereof (for example maltodextrins), lactose, mannitol and calcium disphosphate, as lubricants are stearates of aluminum and calcium, talc or silicones, as flow aids are magnesium stearate, colloidal silica, talc or Aerosil, as plasticizers are low molecular weight polyalkylene oxides, low molecular weight organic plasticizers such as glycerol, pentaerythritol, glycerol monoacetate, diacetate or triacetate, propylene glycol, sorbitol or Na diethyl sulfonsuccinate, as colorants are azo dyes, (in)organic pigments or natural coloring agents, or other conventional excipients such as sugar (alcohols), polymers, phosphates and surfactants, which if needed ought in each case preferably to be present in concentrations between 0.02 and 50% by weight in

relation to the total weight of the sustained release form.

Finally, besides special sustained release compositions, the present invention also provides preferred sustained release forms which are produced by a particular process:

For the sustained release form of the invention it is possible, for example, for commercially available chitosan as normally obtained from shrimp shells first to be swollen in acid aqueous solution and then to be homogenized with crystalline α-lipoic acid and, after addition of the acid, wet-granulated. Tablets are then compressed by conventional methods from the dried granules. The proportion of α-lipoic acid by weight in such tablets can in this case be more than 75%.

However, a procedure which is to be preferred according to the invention in this connection is one in which

1) component (a) is mixed with component (c), preferably in the ratio 1:2 to 1:4 by weight, then water is added to this mixture, and the resulting mixture is homogenized for example as solution with the α-lipoic acid component (b) in the preferred mixture:component (b) ratio of 1:0.3-0.003 by weight,
2) the homogenate from 1) is subjected to a wet granulation, and the granules are dried preferably at temperatures between 5 and 50°C, particularly preferably between 25 and 40 C°, and
3) the dry granules are tableted.

The α-lipoic acid or derivatives thereof which has/have been homogenized with chitosan or another cationogenic polymer which is suitable according to the invention and the acid component (c), and wet-granulated and tableted can, however, also be produced by any other

process. This is because in this connection it is in particular immaterial whether the α-lipoic acid (derivatives) have been produced for example by recrystallization with an organic solvent or solvent mixture or whether the crude α-lipoic acid is employed without any organic solvent.

Because of the favorable properties of the sustained release form of the invention, its use as food supplement is claimed just as preferably as the use as medicament and/or cosmetic, it being possible to employ the sustained release form for oral, dermal, parenteral, rectal, vaginal or local (topical) administrations.

Also provided within the framework of the present invention is the use of the claimed sustained release form as gels, semisolid dosage forms or solid solutions or else as base for producing gels, solid solutions and, in particular, semisolid dosage forms.

The following figures and examples demonstrate the advantages of the sustained release form of the invention. These show

Fig. 1 interactions between cationogenic chitosan (as example of component a)), anionogenic α-lipoic acid (component b)) and another acid component (c) (depicted as anion $A^{\ominus}$);

Fig. 2 comparison of the effect of chitosan and acetic acid on the sustained release of α-lipoic acid (the studies of α-lipoic acid diffusion were carried out without chitosan, with chitosan, with chitosan 1/4 acetate, with chitosan 1/2 acetate and with chitosan 1/1 acetate. The indicated values are means (± SD) of at least three single experiments and

Fig. 3 the profile of release from α-lipoic acid/chitosan tablets (α-lipoic acid content > 75%)

Examples

1. Diffusion study

In order to ensure delayed release of α-lipoic acid over a period of 24 hours from the dosage form, chitosan was employed as polymeric carrier matrix for the active ingredient. Because of ionic interactions of this cationogenic polymer with the anionogenic active ingredient α-lipoic acid, the latter is released continuously. In this diffusion study, the effect of chitosan on the diffusion characteristics of α-lipoic acid was investigated. The results of this investigation are depicted in Fig. 2 and illustrate the strong effect of the cationogenic polymer on the diffusion characteristics of the active ingredient. Whereas the concentration equilibrium of α-lipoic acid inside and outside the dialysis vessel was attainable within about 5 hours without chitosan, only 63.8% ± 4.3% of this equilibrium were attained in the presence of the cationogenic polymer chitosan. On the one hand, chitosan can be hydrogenated only in ionic form in aqueous solutions and, on the other hand, preceding studies have shown unambiguously that α-lipoic acid is too hydrophobic as counterion to bring about sufficient swelling of the polymer. As this diffusion study shows, addition of a rather polar acid additionally to the active ingredient is necessary in order to ensure hydration of the polymer.

Because of its comparatively high pKa of about 4.76, which permits ionic bonding of the active ingredient,

gives rise to no toxic risks and ensures excellent hydration of chitosan, acetic acid was chosen.

As shown by the results of the diffusion study, even low concentrations of acetic acid bring about an increased effect of chitosan sustaining the release of the active ingredient α-lipoic acid: the occupation of every fourth amino group with chitosan with acetic acid (chitosan 1/4 acetate) led to a significant reduction in the rate of release of α-lipoic acid from the polymer. One reason for this observation may be regarded as being an increase in free primary amino groups in the chitosan, which are accessible to the active ingredient, this being attributable to the higher degree of hydration caused by the acetic acid.

As soon as the acetic acid reaches a concentration which make all the primary amino groups of the polymer accessible to the active ingredient it is no longer possible to increase the release-sustaining effect of the polymer.

On the other hand, further addition of acetic acid appears to reduce the release-sustaining effect because the latter was significantly less at 39.8 ± 0.9% with a chitosan/acetate ratio = 1:1 over a period of 5 hours than with a chitosan to acetate ratio = 1:2 (31.4 ± 2.8%).

This observation may be explained by a competing behavior of the active ingredient α-lipoic acid and the acetic acid for the freely accessible amino groups of the polymer. It should be noted, finally, that larger amounts of the active ingredient are removed from the polymer as the addition of acetic acid increases.

2. Release study

Investigations of the profile of release from the tablets were carried out by internationally recognized methods as are to be found, for example, in the European pharmacopoeia.

Example 1

5 g of chitosan from shrimp shells with a degree of deacetylation of more than 85% were swollen in 10 ml of glacial acetic acid and 65 ml of demineralized water at room temperature for 24 hours. This mixture was then homogenized with 24 g of α-lipoic acid and wet-granulated. The granules were dried at 40°C and subsequently compressed to tablets with a diameter of 10 mm and a weight of 400 mg (Korsch, type EKO-DMS, Berlin, Germany). The content of α-lipoic acid in these tablets was more than 75% (m/m).

Example 2

50 g of chitosan from shrimp shells with a degree of deacetylation of more than 85% were swollen in 100 ml of glacial acetic acid and 750 ml of demineralized water at room temperature for 24 hours. This mixture was then homogenized with 50 g of α-lipoic acid and wet-granulated. The granules were dried at 40°C and subsequently compressed to tablets with a diameter of 10 mm and a weight of 400 mg (Korsch, type EKO-DMS, Berlin, Germany). The content of α-lipoic acid in these tablets was about 50% (m/m).

Result of tests

Release tests with these tablets showed a strong sustaining of release through the combined use of α-lipoic acid with chitosan. The dissolution profile of the α-lipoic acid/chitosan tablets (400 mg) in 600 ml of demineralized water at 37°C is depicted in Fig. 3.

The values shown are means from three release studies with the corresponding standard deviations. This release corresponds approximately to one of 0 order during the first 8 hours. The sustaining of release shown, with which only 80% of α-lipoic acid are released after 22 hours, was chosen because, on the one hand, this release in vivo is speeded up by a high electrolyte concentration and, on the other hand, part of the α-lipoic acid is absorbed even in the colon.